PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To
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PCT

WRITTEN OPINION

(PCT Rule 66)

Applicant's or agent's file reference 312762002440	Date of Mailing (*day/month/year*) REPLY DUE within 1 months/days from the above date of mailing

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US00/33645	11 December 2000 (11.12.2000)	10 December 1999 (10.12.1999)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): A61K 48/00; C12N 15/00 and US Cl.: 514/44; 435/320.1; 435/455

Applicant

ANTICANCER, INC.

1. This written opinion is the first (first, etc,) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- [x] I Basis of the opinion
- [ ] II Priority
- [ ] III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] IV Lack of unity of invention
- [x] V Reasoned statement under Rule 66.2 (a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] VI Certain documents cited
- [ ] VII Certain defects in the international application
- [ ] VIII Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension. See rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 *bis*.
For an informal communication with the examiner, see Rule 66.6

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 10 April 2002 (10.04.2002).

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Daniel M Sullivan Telephone No. 703-308-0196

WRITTEN OPINION

International application No.
PCT/US00/33645

I. Basis of the opinion

1 With regard to the **elements** of the international application:*

[·] the international application as originally filed

[·] the description:
pages 1-19, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

[·] the claims:
pages 20-22, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

[·] the drawings:
pages 1-3, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

[ ] the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages NONE _____

[ ] the claims, Nos. NONE _____

[ ] the drawings, sheets/~~fig~~ NONE _____

5. [ ] This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed."*

WRITTEN OPINION

International application No.
PCT/US00/33645

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 STATEMENT

Novelty (N)	Claims	1-9,12,14,16,18 and 19	YES
	Claims	10,11,13,15,17,20 and 21	NO
Inventive Step (IS)	Claims	12, 16, 18 and 19	YES
	Claims	1-11, 13-15, 17, 20 and 21	NO
Industrial Applicability (IA)	Claims	1-21	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS
Please See Continuation Sheet

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

TIME LIMIT
The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

V. 2. Citations and Explanations:
Claims 10, 15, 17, 20 and 21 lack novelty under PCT Article 33(2) as being anticipated by Li *et al.* (1997) US Patent No. 5,641,508.

Li *et al.* teaches a method of delivering a nucleic acid to a hair follicle wherein the hair follicle is comprised within a fragment of skin maintained in histoculture that is treated with said nucleic acid (see especially column 5, paragraphs 1-3 for a description of the histocultured skin, and Example 3, beginning in column 26, for a description of gene transfer into the histocultured skin). Li *et al.* also teaches a histoculture modified to contain a heterologous nucleic acid wherein the histoculture is an intact fragment of skin and contains a modified hair follicle (see especially Example 3 c. "Delivery and Expression of Beta-Galactosidase Gene in Hair Follicles of Histocultured Skin" beginning in column 29, and Figure 5). Finally, in the first paragraph of column 5, Li *et al.* teach that the histocultured skin allows the growth of hair shafts in the follicle cells, indicating that the hair follicle is in anagen phase. The modified histoculture containing a heterologous nucleic acid and method of delivering a nucleic acid to an intact histoculture taught by Li *et al.* are the same as those taught in the instant application, therefore the claims are anticipated by Li *et al.*

Claims 11, 13, 17 and 20 lack novelty under PCT Article 33(2) as being anticipated by either one of Poston *et al.* (1998) *J Thoracic Cardiovasc Surg* 116:386-396 or Chapelier *et al.* (1996) *Hum Gene Ther* (1996) 7:1837-1845.

Chapelier *et al.* teaches a method of delivering a nucleic acid to intact lung tissue comprising treating a histoculture (i.e. the graft stored in a basin of physiologic saline solution) with a nucleic acid comprised within an adenovirus vector (see especially the final paragraph on page 1838). Chapelier *et al.* further teaches grafting the histocultured modified lung tissue into a recipient mammal (see especially the first paragraph on page 1839). The method of introducing a nucleic acid into an intact tissue and into a mammalian subject, as well as the histoculture modified to contain a heterologous nucleic acid, taught by Chapelier *et al.* are the same as those claimed in the instant application.

Poston *et al.* teach a method of delivering a nucleic acid to intact heart tissue comprising treating a histoculture (i.e. explanted heart in phosphate buffered saline) with a nucleic acid (i.e. antisense oligonucleotide; see especially the first full paragraph on page 388). Poston *et al.* further teaches transplanting the modified histocultured heart tissue into a recipient animal (see especially the paragraph bridging pages 387 and 388). The method of introducing a nucleic acid into an intact tissue and into a mammalian subject, and the histoculture modified to contain a heterologous nucleic acid taught by Poston *et al.* are the same as those taught in the instant application. Therefore, the limitations of the claims are anticipated by the prior art.

Claims 1-9 and 14 lack an inventive step under PCT Article 33(3) as being obvious over Li *et al.* (*supra*) in view of Naughton and Naughton (1993) US Patent No. 5,266,480 and further in view of Weiner *et* al.WO 98/46208. The teachings of Li *et al.* are recited

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

above. Li *et al.* do not teach transplanting the modified histoculture back onto a patient. Naughton and Naughton teach that histocultured skin and hair follicles can be transplated back into a recipient (see especially the second paragraph of column 9, and column 33). Weiner *et a.* .teaches the desirability of delivering nucleic acids to the hair follicle. Therefore it would have obvious to one of ordinary skill in this art at the time this invention was made to transplant the modified follicles of Li *et al.* according to the teachings of Naughton and Naughton.

Claims 12, 16, 18 and 19 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest treatment of a histoculture with collagenase prior to modifying said histoculture with a nucleic acid.

---------- NEW CITATIONS ----------

US 5,266,480 A (NAUGHTON et al) 30 November 1993, see entire document.

US 5,641,508 A (LI et al) 24 June 1997, see entire document.

CHAPELIER et al. Gene therapy in lung transplantation: feasibility of ex vivo adenovirus-mediated gene transfer to the graft. HUMAN GENE THERAPY, vol. 7, 1996, pages 65-69, see entire document.

POSTON et al. Ex vivo gene therapy prevents chronic graft vascular disease in cardiac allografts" J THROAC CARDIOVASC SURG, Vol. 116, 1998, pages 389-396, see entire document.